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Review

Ozonated olive oil effects in dentistry: A randomized clinical trial systematic review

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Abstract: *Background:* Ozonated olive oil (OOO) is emerging as a significant therapeutic agent in dentistry, leveraging its antimicrobial, anti-inflammatory, and healing properties to enhance oral health outcomes. This review synthesizes findings from recent randomized controlled trials to assess the efficacy of OOO in various dental applications, including managing peri-implant mucositis, caries, periodontal disease, and endodontic infections. *Methods:* According to the PRISMA guidelines, five studies were included in this systematic review, having met our inclusion criteria. *Results:* The studies collectively demonstrate that OOO effectively reduces clinical parameters such as bleeding on probing and probing depth and enhances microbial control in periodontal therapy and root canal treatments. Additionally, OOO's application has significantly improved dentin hypersensitivity, particularly when combined with calcium sodium phosphosilicate. *Conclusions:* The results emphasize OOO's promise as a supplementary treatment option, showcasing its capacity to enhance tissue healing while reducing dependence on conventional antibiotics. Further research is necessary to confirm these findings and

establish standardized treatment protocols aimed at optimizing the use of OOO in clinical settings.

Keywords: olive oil; randomized controlled trial; ozone therapy; oral health

1. Introduction

Dental plaque and gingivitis are prevalent oral health issues that, if neglected, may advance to tooth loss and possibly other systemic diseases [1]. In addition to traditional medications, novel therapeutic approaches are being evaluated to prevent periodontal destruction and facilitate the regeneration of periodontal tissues [2,3]. Multiple clinical trials and systematic reviews have examined the efficacy of herbal and ozonated oral care regimens in minimizing plaque and gingivitis [4–7]. Nevertheless, their results are disparate, lack consistency, and require more concrete evidence.

Ozonated olive oil (OOO) is increasingly recognized in dental medicine for its unique capabilities in managing various oral health conditions. This therapeutic agent leverages the potent antimicrobial effects of ozone with the anti-inflammatory and emollient properties of olive oil, providing a biocompatible treatment option that aligns well with the demands of minimally invasive and patient-centered dental care. Ozonated olive oil's primary benefits are seen across a spectrum of applications, including the management of peri-implant mucositis, caries, periodontal disease, and endodontic infections, where it can offer sustained antimicrobial action, promote tissue healing, and reduce reliance on conventional antibiotics [8]. The mechanism of OOO is based on its gradual ozone release upon contact with tissue, allowing for extended microbial control while minimizing cytotoxicity. In peri-implant care, for instance, OOO is used to manage peri-implant mucositis by reducing the microbial load around implants. Studies demonstrate that this application helps prevent further complications and promotes healing of the soft tissues surrounding implants, enhancing their stability and long-term success [9,10].

In periodontal therapy, OOO has shown significant benefits in reducing inflammation and bacterial colonization, particularly in conditions like periodontitis where inflammation and bacterial biofilms play a central role. The slow-release ozone action of OOO directly combats pathogenic bacteria, such as *Porphyromonas gingivalis* and *Tannerella forsythia*, without irritating gingival tissues [11].

OOO represents an option for treating gingivitis and periodontitis, as well as in furcation areas that are otherwise challenging to reach with conventional treatments. Furthermore, OOO has been explored as an adjunct in caries management, where its antibacterial properties provide a preventive effect against caries-causing bacteria. Its application on carious lesions can reduce bacterial presence and may also help desensitize exposed dentin, making it suitable for patients with dental hypersensitivity following demineralization treatments [12].

In endodontic therapy, OOO shows promise in managing root canal infections by targeting resistant pathogens such as *Enterococcus faecalis*, a bacterium commonly implicated in post-treatment endodontic failures. Studies show that OOO can be a potent adjunct to traditional endodontic disinfectants, offering additional microbial control in areas where conventional irrigants may not fully penetrate. By incorporating OOO in endodontic protocols, clinicians can leverage its sustained antimicrobial action to improve treatment outcomes and reduce the likelihood of reinfection [13,14].

While olive oil is the primary focus due to its compatibility and effectiveness in dental applications, other ozonated oils, such as sunflower and coconut oils, have also demonstrated benefits.

Ozonated sunflower oil has strong antimicrobial properties and could be considered for applications requiring rapid pathogen reduction, though it lacks the regenerative benefits specific to olive oil. Ozonated coconut oil, on the other hand, contains high levels of lauric acid, which naturally contributes to antifungal activity and could be beneficial in managing *Candida* infections, particularly in patients with denture-related stomatitis [15,16].

This manuscript aims to highlight the effect of ozonated olive oil on oral health through a systematic review of randomized clinical trials (RCTs).

2. **Materials and methods**

2.1. Eligibility criteria

Studies included in this systematic review met several criteria: they involved OOO or other ozonated oils in a clinical or in vitro setting, targeted specific oral health conditions (such as periodontitis, endodontic infections, and dentin hypersensitivity), and reported on efficacy and safety outcomes. Studies were excluded if they used ozone in a form other than oil (e.g., ozonated water or gas) without comparison to ozonated oils or lacked adequate data on methods and results. Studies that did not focus on oral or dental applications were excluded to maintain the scope of the review. This study was conducted according to PRISMA guidelines.

2.2. Information sources

Primary electronic databases utilized included PubMed, Scopus, and Google Scholar.

2.3. Search strategy

For this systematic review article, a literature search was conducted to examine the therapeutic effects of ozonated oils, particularly ozonated olive oil (OOO), in dentistry and medical applications. Search terms incorporated “ozonated olive oil”, “ozone therapy”, “dental applications of ozone”, “ozone in endodontics”, “periodontal ozone therapy”, and “ozone in oral health”, both as individual terms and in combination.

2.4. Selection process

Articles published in English between 1995 and 2023 were considered, focusing on peer-reviewed journal articles, clinical trials, in vitro studies, and systematic reviews.

2.5. Data collection process

Two independent reviewers initially screened titles and abstracts for relevance (F. Go and F. Ga). They then retrieved full texts for studies that appeared to meet inclusion criteria or for which relevance was unclear. Data extraction was performed using a standardized form that captured study design, sample size, intervention type, application protocol, primary outcomes, and conclusions. Discrepancies in study inclusion and data extraction were resolved through discussion with a third reviewer (C.D.A.).

2.6. Data items

Table 1. Comparative sample sizes, outcomes, and key findings from five RCTs on ozonated olive oil in dentistry. OOO = ozonated olive oil; CHX = chlorhexidine; ZnO = zinc oxide. Data include mean values ± SD where reported, and significance levels for group comparisons.

Study (Year)	Sample and groups	Outcomes measured
Choudhary et al. [8] (2024)—Peri-implant mucositis	50 patients (2 groups; n = 25 each: OOO gel vs. 0.2% chlorhexidine gel)	Plaque Index (PI; Silness-Löe), Gingival Index (GI; Löe-Silness) at baseline and 4 weeks
El-Desouky et al. [9] (2023) Primary tooth pulpectomy	90 primary molars (3 groups; n = 30 each): root canals filled with ZnO + OOO vs. ZnO + plain olive oil vs. ZnO + eugenol (ZOE)	Clinical success (absence of pain, swelling, mobility), radiographic healing (furcation radiolucency resolution via bone density increase, PDL space width) at 3, 6, and 12 months
Nardi et al. [10] (2020) Periodontitis adjunctive therapy	96 patients (2 groups; n = 48 each): SRP + OOO-based mouthwash vs. SRP + water (control); follow-up at 14 days and 1, 3, and 6 months	Plaque Index (PI), Bleeding on Probing (BoP), Probing Pocket Depth (PPD), salivary MMP-8 (ng/mL) at baseline and follow-ups
Patel et al. [11] (2013) Post-surgical dentin hypersensitivity	51 patients (split into 4 groups after periodontal surgery): A, OOO alone (n = 11); B, OOO + calcium sodium phosphosilicate (NovaMin) paste (n = 14); C, placebo oil + NovaMin (n = 13); D, placebo oil alone (n = 13). Sensitivity was assessed immediately post-op and at multiple follow-ups	Dentin hypersensitivity (pain to stimuli) measured by 100 mm Visual Analog Scale (VAS) at individual tooth level and overall (global) score; SEM analysis of dentinal tubule occlusion on extracted samples
Patel et al. [12] (2012) Chronic periodontitis therapy	20 mouth patients (split-design; 4 treatments per subject on different quadrants): A, Scaling and root planing (SRP) alone; B, SRP + subgingival OOO application; C, OOO alone (no SRP); D, 0.2% chlorhexidine gel alone. Outcomes assessed at 2, 4, 6, and 8 weeks	Clinical: PI, Gingival Index (GI), Sulcus Bleeding Index (SBI), PPD, Clinical Attachment Level (CAL); Patient-reported pain/discomfort (VAS); microbiological: total subgingival bacterial counts and presence of 8 periodontal pathogens (by PCR)

Data items extracted from the selected studies included authors, year of publication, study design, sample size, demographic characteristics of participants, type of intervention (formulation of ozonated olive oil, concentration, frequency and duration of application), comparator(s), clinical and microbiological outcome measures (e.g., plaque index (PI), bleeding on probing (BoP), probing pocket depth (PPD), clinical attachment level (CAL), visual analog scale (VAS) scores for sensitivity, radiographic parameters such as periodontal ligament space, and bone radiodensity), biochemical markers (e.g., matrix metalloproteinase-8 (MMP-8)), follow-up duration, and statistical methods and significance reported for each manuscript (Table 1).

2.7. Risk of bias assessment

Two independent reviewers (F. Go and F. Ga) assessed the risk of bias for the included studies using the Cochrane Collaboration's Risk of Bias (RoB) tool for randomized trials. The following domains were evaluated: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential biases. Each domain was judged as "low risk", "high risk", or "unclear risk" of bias based on the information reported in the manuscripts. Any reviewer discrepancies were resolved through discussion and consensus with a third independent reviewer (T.N.).

2.8. Synthesis methods

The synthesis of evidence followed a narrative approach due to the clinical heterogeneity in the interventions, outcomes, and study methodologies. A descriptive summary was structured to highlight findings across the various applications of ozonated olive oil in dentistry. Quantitative synthesis (meta-analysis) was not performed owing to methodological and clinical variability among the studies (e.g., differing intervention protocols, outcome measurements, and follow-up durations). Instead, the results were systematically organized into comparative tables to summarize and visually interpret the clinical effectiveness, microbiological impact, and safety profile of ozonated olive oil across the included studies.

3. Results

3.1. Study selection

Out of the 320 studies identified, 47 articles met the initial inclusion criteria. After further screening for relevance to dental applications and therapeutic outcomes, 17 articles were selected for detailed review. Five manuscripts met all criteria following full-text evaluation and were included in the final synthesis. The PRISMA flow diagram illustrates this process, outlining the stages from identification to final inclusion and the reasons for exclusion at each stage (Figure 1).

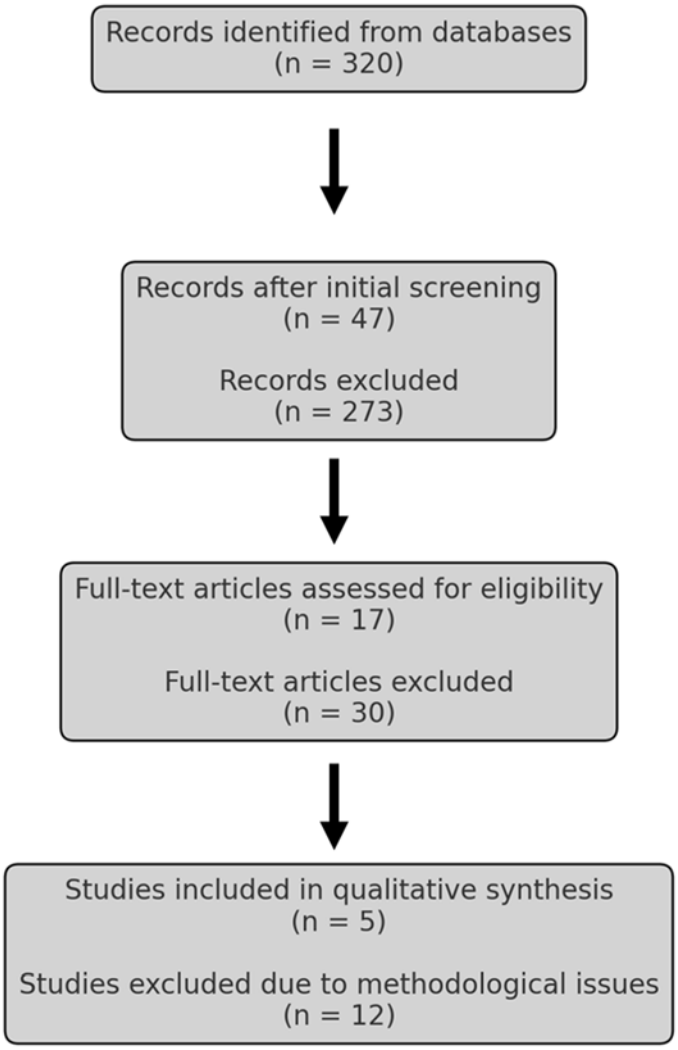

Figure 1. PRISMA flow chart.

3.2. Study characteristics

The clinical study by Choudhary et al. [8] involved patients diagnosed with peri-implant mucositis treated with OOO gel applied topically to the peri-implant tissues. The gel was applied to the affected peri-implant mucosa following a standardized application protocol that specified the frequency and duration for all participants. To assess the efficacy of the treatment, clinical parameters such as bleeding on probing (BoP), probing depth (PD), and plaque index (PI) were recorded at baseline and during follow-up visits.

El-Desouky et al.'s [9] randomized controlled trial included 90 non-vital primary molars from children aged 4–8 years, which were randomly assigned into three groups (n = 30 per group) based on the root canal filling material used. Group I received zinc oxide mixed with OOO, Group II received zinc oxide mixed with olive oil, and Group III received zinc oxide-eugenol (ZOE). After administering local anesthesia and applying rubber dam isolation, standard pulpectomy procedures were performed. The root canals were instrumented using K-files up to size 35, followed by irrigation with 2.5% sodium

hypochlorite and normal saline, and the canals were dried with paper points. The respective filling materials were prepared by mixing zinc oxide powder with the designated liquid (OOO, olive oil, or eugenol) to achieve a creamy consistency, and the prepared paste was introduced into the canals using a lentulo spiral, ensuring complete filling without overextension. Lastly, the access cavities were sealed with glass ionomer cement, and stainless steel crowns were placed as final restorations. Clinical and radiographic evaluations were conducted at 3, 6, and 12 months post-operatively to assess treatment outcomes.

The randomized clinical trial by Nardi et al. [10] enrolled 96 patients diagnosed with periodontitis, who were randomly assigned to two groups: the study group underwent scaling and root planing (SRP) combined with the use of an ozonated olive oil-based mouthwash, while the control group underwent SRP alone. All participants received SRP performed by experienced periodontists, with the study group instructed to use the OOO mouthwash twice daily for 3 months, while the control group did not use any adjunctive mouthwash. Salivary samples were collected at baseline (T0), 14 days (T1), 1 month (T2), and 6 months (T3) to measure MMP-8 levels, and periodontal indices, including plaque index (PI), bleeding on probing (BoP), and probing pocket depth (PPD), were also recorded at these time points.

The study by Patel et al. [11] was designed as a double-blinded, randomized controlled trial involving patients experiencing root dentin hypersensitivity following periodontal surgery. Participants were randomly assigned to one of three groups: Group A received the application of OOO, Group B received OOO followed by calcium sodium phosphosilicate, and Group C received a placebo treatment. After periodontal surgery, the assigned treatments were applied to the exposed root surfaces, with OOO being applied using a microbrush. This application was followed by calcium sodium phosphosilicate in Group B, while the placebo group received a sham treatment. Dentin hypersensitivity was assessed using a visual analog scale (VAS) at baseline, immediately after treatment, and during subsequent follow-up visits.

Another study by Patel et al. [12] involved a double-blinded, randomized controlled trial that included patients with chronic periodontitis randomly assigned to either the test or the control group. The test group received a subgingival application of OOO, while the control group received a placebo. Following initial periodontal therapy, the participants in the test group received the OOO through a syringe with a blunt needle, and similar applications were performed for the control group. These applications occurred at baseline and were repeated at specified intervals. To assess the outcomes, clinical parameters such as probing pocket depth (PPD), clinical attachment level (CAL), and bleeding on probing (BoP) were measured at both the baseline and at follow-up visits.

As can be observed in Table 2, the studies focusing on the management of peri-implant mucositis indicate a significant reduction in clinical inflammation parameters, such as bleeding on probing and probing depth. The consistent improvement in these parameters across multiple studies suggests that OOO gel is effective in promoting implant stability and reducing inflammation.

Table 2. Key outcomes of the study.

Study	Application area	Study design	Key results	Key outcomes
Choudhary et al. [8]	Peri-implant mucositis	Randomized controlled trial	Within-group: Both OOO and CHX groups showed significant reductions in mean PI and GI after 4 weeks ($p < 0.05$). Between-group: No statistically significant differences between OOO and CHX in PI or GI improvement ($p > 0.05$). Ozonated olive oil gel was equally effective as chlorhexidine for peri-implant mucositis management.	Significant reduction in BoP, PI, and PD with ozonated olive oil gel.
El-Desouky et al. [9]	Root canal filling in molars	Randomized controlled trial	Clinical: High 12-month success in all groups (92.6% OOO, 92.9% olive oil, 82.1% ZOE); difference not significant ($p = 0.346$). Radiographic: OOO group showed significantly greater furcation bone density increase (bone fill) at 3, 6, and 12 months compared to ZOE ($p < 0.05$). All groups had decreased periodontal ligament (PDL) space over time; between-group differences in PDL space narrowing were not significant. Overall, the ZnO–OOO paste promoted superior radiographic healing (bone regeneration) relative to ZOE, with comparable clinical outcomes among groups.	Improved furcation radiodensity and reduced periodontal ligament space.
Nardi et al. [10]	Periodontal therapy	Randomized clinical trial	Within-group: Both groups had significant improvement in PI (%), BoP (% sites), and PPD (mm) from baseline to 6 months ($p < 0.05$). Mean PPD dropped from ~4.4 to ~2.1 mm with OOO vs. from 4.4 to 2.45 mm in control. Between-group: By 6 months, PI and PPD improvements were similar (no significant difference). MMP-8 levels fell markedly in the OOO group (from 82.3 ± 54.4 to 32.3 ± 27.8) vs. a smaller decrease in controls (from 128.8 ± 30.7 to 94.3 ± 26.9), with OOO yielding a significantly greater reduction in inflammatory MMP-8 ($p < 0.001$). BoP reduction was comparable, though at 6 months the control showed a slightly greater decrease in bleeding sites ($p = 0.04$). Conclusion: Ozonated olive oil mouthwash as an adjunct to SRP led to greater suppression of MMP-8 (reflecting reduced inflammation) and similar clinical improvements in plaque, bleeding, and pocket depth compared to SRP alone.	Significant reduction in salivary MMP-8 levels with ozonated olive oil.

Continued on next page

Study	Application area	Study design	Key results	Key outcomes
Patel et al. [11] (2013)	Dentin hypersensitivity	Randomized, double-blinded, controlled trial	Group B (OOO + NovaMin) achieved the largest decrease in mean sensitivity scores over time (tooth-level and global), highly significant within-group reduction ($p < 0.001$), and significantly lower sensitivity than other groups by the end of the study ($p < 0.001$). Group C (NovaMin only) also had significant sensitivity reduction vs. baseline ($p < 0.001$). In contrast, Group A (OOO alone) did not differ significantly from Group D (placebo) ($p > 0.05$). OOO by itself did not appreciably reduce post-surgery hypersensitivity. Scanning EM showed Group B specimens with the greatest dentinal tubule occlusion (significantly more closed tubules, $p < 0.001$, vs. others). Conclusion: Ozonated olive oil requires combination with a bioactive desensitizer (NovaMin) to effectively relieve root dentin sensitivity; OOO monotherapy was not efficacious for sensitivity in this model.	Significant reduction in VAS scores; combination therapy most effective.
Patel et al. [12] (2012)	Chronic periodontitis	Randomized, controlled, double-blind study	Within-subject: Adjunctive OOO + SRP (B) yielded the greatest improvement in clinical indices and attachment gain over 8 weeks. For example, PPD reduction was significantly larger with OOO+SRP vs. SRP alone (mean PPD reduction 2.30 mm vs. 1.75 mm, $p < 0.001$, as reported) and greater CAL gain. OOO monotherapy (C) also showed significant improvements in PPD, GI, and bacterial reduction vs. baseline ($p < 0.001$), though not as much as SRP-based therapy. Microbiologically, OOO (alone or with SRP) led to a greater decrease in total bacterial counts and frequency of pathogens compared to controls. Adverse effect: OOO + SRP was associated with a significant increase in post-treatment dentinal hypersensitivity ($p < 0.05$) in those quadrants, an undesirable side effect not seen with other treatments. Overall, OOO as an adjunct to SRP (and even alone) significantly improved periodontal parameters and reduced bacterial load compared to SRP or CHX alone, but its use with SRP may transiently heighten tooth sensitivity.	Significant improvements in clinical parameters and reduction in bacterial counts.

3.3. Risk of bias in studies and reporting biases

All included studies were randomized controlled trials; however, the risk of bias varied among them. Random sequence generation and allocation concealment methods were generally well-reported, reflecting a low risk of selection bias in most studies. Blinding of participants and personnel was explicitly mentioned and adequately performed in four out of the five studies, indicating a predominantly low risk of performance bias; however, the potential risk of performance bias remained unclear in one study due to incomplete reporting on blinding procedures. Blinding of outcome assessment was consistently reported and maintained across the studies, minimizing detection bias. Attrition bias was generally low, with minimal loss to follow-up and adequate reporting of missing data handling. Selective outcome reporting appeared minimal, as predefined primary and secondary outcomes in study protocols were typically reported. No significant reporting biases were identified through analysis of available manuscripts and protocols. Overall, the studies included in this review demonstrated an acceptable methodological quality, with predominantly low or unclear risks of bias across assessed domains.

3.4. Results of individual studies

In Choudhary et al. [8], the application of OOO gel resulted in significant reductions in bleeding on probing (BoP), probing depth (PD), and plaque index (PI) compared to baseline values, with these improvements observed at subsequent follow-ups, indicating the treatment's efficacy in managing peri-implant mucositis. Furthermore, the use of OOO gel proved effective in treating peri-implant mucositis, leading to enhancements in the clinical parameters associated with inflammation of peri-implant tissues.

Clinical outcomes across all three groups exhibited significant improvements in clinical signs and symptoms at the 3-, 6-, and 12-month follow-up, with no statistically significant differences observed regarding clinical success among the groups. In El-Desouky et al. [9], in terms of radiographic outcomes, the group treated with zinc oxide and OOO demonstrated a significant increase in radiodensity in the furcation area and a reduction in periodontal ligament space at the same follow-up intervals compared to the other groups, suggesting enhanced bone healing and reduced periapical inflammation. In conclusion, the use of zinc oxide combined with OOO as a root canal filling material in primary molars showed comparable or superior clinical and radiographic success when compared to zinc oxide with olive oil or eugenol, indicating that it can be considered a viable alternative for pulpectomy in infected primary teeth.

In Nardi et al. [10], both groups exhibited significant reductions in plaque index (PI), bleeding on probing (BoP), and probing pocket depth (PPD) at the 14-day, 1-month, and 6-month follow-up compared to baseline; however, the group using the ozonated olive oil-based mouthwash showed significantly greater improvements in these parameters than the control group. In terms of biochemical outcomes, salivary MMP-8 levels decreased significantly in both groups over the study period, but the group using the ozonated olive oil-based mouthwash demonstrated a significantly greater reduction in MMP-8 levels compared to the control group, indicating a decrease in inflammatory activity. In conclusion, the adjunctive use of an ozonated olive oil-based mouthwash with non-surgical periodontal therapy led to superior clinical and biochemical improvements compared to mechanical therapy alone, suggesting an additional beneficial effect in controlling periodontal inflammation.

Patel et al. [11] showed that all groups experienced significant reductions in post-surgical root dentin hypersensitivity immediately after treatment and at subsequent follow-ups; however, the group receiving the combined application of ozonated olive oil and calcium sodium phosphosilicate exhibited a significantly greater reduction in sensitivity compared to the other groups. Therefore, the topical application of OOO, particularly when combined with calcium sodium phosphosilicate, is effective in reducing post-surgical root dentin hypersensitivity, offering a viable therapeutic option for managing this condition.

In Patel et al. [12], both groups showed significant improvements in clinical parameters, including reductions in probing pocket depth (PPD), gains in clinical attachment level (CAL), and decreases in bleeding on probing (BoP). However, the group receiving subgingival application of OOO exhibited significantly greater improvements in these parameters compared to the control group. Microbiological analysis revealed a significant reduction in periodontal pathogens in the treated group, indicating an enhanced antimicrobial effect of the OOO application. Subgingival application of OOO as an adjunct to conventional periodontal therapy resulted in superior clinical and microbiological outcomes in the treatment of chronic periodontitis, suggesting its potential as an effective adjunctive treatment modality.

As can be observed in Table 3, the outcomes of studies assessing the role of OOO in periodontal therapy and dentin hypersensitivity reveal that OOO-based mouth rinses produced superior clinical and biochemical improvements compared to traditional mechanical therapy alone. This highlights the potential of OOO as an adjunctive treatment for managing periodontal inflammation. Furthermore, the table illustrates that the combination of OOO with sodium calcium phosphosilicate resulted in a more pronounced reduction in post-operative discomfort related to dentin hypersensitivity, supporting OOO's versatility in clinical practice.

3.5. Synthesis results

Table 3. Main statistical results.

Study	Main results
Choudhary et al. [8]	The significant reduction in bleeding on probing (BoP), plaque index (PI), and probing depth (PD) in the treatment group suggests a positive effect of ozonated olive oil gel in managing peri-implant mucositis.
El-Desouky et al. [9]	The observed increase in furcation radiodensity and decrease in periodontal ligament space in the zinc oxide-ozonated olive oil group indicate its potential efficacy as a root canal filling material in primary molars.
Nardi et al. [10]	The significant reduction in salivary matrix metalloproteinase-8 (MMP-8) levels in the ozonated olive oil mouthwash group suggests anti-inflammatory effects beneficial in periodontal therapy.
Patel et al. [11] (2013)	The significant reduction in visual analog scale (VAS) scores for dentin hypersensitivity in both treatment groups, with the combination therapy showing the most pronounced effect, indicates the potential benefit of ozonated olive oil in managing dentin hypersensitivity.
Patel et al. [12] (2012)	The significant improvements in clinical parameters and reduction in pathogenic bacterial counts in the ozonated olive oil group suggest its potential as an adjunctive treatment in chronic periodontitis.

In summary, the consistent positive outcomes across these studies highlight the potential of OOO as an effective adjunctive treatment in various dental applications.

4. Discussion

The application of ozone therapy in dentistry and maxillofacial surgery has been extensively explored, with numerous studies highlighting its antimicrobial, anti-inflammatory, and healing properties. This discussion synthesizes findings from key publications to provide a comprehensive overview of ozone's efficacy and potential applications in dental and oral medicine. Ozone's potent antimicrobial properties have been demonstrated against a variety of oral pathogens. Arita et al. [13] investigated the microbicidal efficacy of ozonated water against *Candida albicans* adhering to acrylic denture plates, revealing significant reductions in fungal viability, thereby suggesting its potential in managing denture-related stomatitis [14].

Similarly, Hems et al. [15] evaluated ozone's ability to eradicate *Enterococcus faecalis*, a bacterium commonly associated with endodontic failures, and found that ozone effectively reduced bacterial counts in vitro, indicating its potential as an adjunctive endodontic disinfectant. In endodontics, ozone therapy has been investigated for its potential to enhance root canal disinfection. Bezrukova et al. [16] reported positive outcomes using medical ozone for root canal treatment, noting improved microbial control and patient outcomes. These findings align with those of Hems et al. [15], who demonstrated ozone's efficacy against *Enterococcus faecalis*, supporting its application in endodontic disinfection protocols. Ozone therapy has been utilized in managing various oral infections due to its broad-spectrum antimicrobial activity. Nogales et al. [17] reviewed ozone therapy's applications in medicine and dentistry, highlighting its effectiveness in treating conditions such as herpes labialis, candidiasis, and other oral infections, thereby underscoring its versatility as a therapeutic modality. The application of ozone in caries management has been explored, particularly concerning root caries. Baysan and Lynch [18] discussed ozone's role in arresting root caries lesions, emphasizing its potential to eliminate cariogenic bacteria and promote remineralization, thus offering a non-invasive treatment option for root caries.

Comparative studies have evaluated ozone therapy against established antimicrobial agents. Parkar et al. [19] conducted a randomized clinical trial comparing the efficacy of ozonated water and chlorhexidine mouth rinse against plaque and gingivitis. The study concluded that both interventions significantly reduced plaque and gingival inflammation, with ozonated water presenting as an effective alternative to chlorhexidine. Bocci [20] provided a comprehensive review of the scientific and medical aspects of ozone therapy, elucidating its biochemical mechanisms, including its ability to modulate oxidative stress and enhance local oxygenation, thereby facilitating tissue healing and antimicrobial effects. The safety profile of ozone therapy has been subject to investigation. Suh et al. [21] reviewed the clinical utility of ozone therapy in dental and oral medicine, noting its favorable safety profile when administered appropriately, with minimal adverse effects reported, thus supporting its integration into clinical practice. Ozonated olive oil (OOO) has garnered significant attention in dentistry due to its antimicrobial, anti-inflammatory, and healing properties. In addition to the five manuscripts previously discussed, numerous studies have explored its efficacy in various dental applications. OOO has potent antimicrobial effects against a broad spectrum of oral pathogens [22]. In dental biofilms, OOO has been investigated for its efficacy in disrupting biofilm formation. A study by Ramzy et al. [23] assessed the adjunctive use of ozonated water in nonsurgical periodontal therapy, demonstrating significant reductions

in plaque index and gingival index compared to conventional therapy alone. While this study utilized ozonated water, it underscores the potential of ozone-based therapies in managing dental biofilms.

Comparative studies and meta-analyses have further elucidated the role of OOO in dental therapy. A systematic review and meta-analysis by Kshitish et al. [24] evaluated the effect of ozone on periodontal pathogens and clinical parameters. In their 2010 study, Kshitish and Laxman conducted a randomized, double-blind, crossover split-mouth trial involving 16 patients diagnosed with generalized chronic periodontitis. The study aimed to compare the clinical and microbiological effects of ozonated water and 0.2% chlorhexidine as subgingival irrigants. The trial was divided into two intervals: the first from baseline to the 7th day, followed by a 4-day washout period, and then a second interval of 7 days. Clinical parameters, including the gingival index and the gingival bleeding index, were assessed alongside microbiological evaluations. The results indicated that both ozonated water and chlorhexidine significantly reduced clinical and microbiological parameters associated with periodontitis. However, ozonated water demonstrated a more pronounced reduction in microbial counts, suggesting its potential as an effective adjunctive treatment in periodontal therapy. The analysis concluded that ozone therapy, including the use of ozonated oils, significantly reduced periodontal pathogens and improved clinical parameters compared to conventional therapy. The safety and biocompatibility of OOO have been assessed in various studies. A study by Sechi et al. [25] evaluated the cytotoxicity of ozonated sunflower oil on human keratinocytes and fibroblasts, reporting no significant cytotoxic effects. While this study focused on sunflower oil, the findings are relevant, as the ozonation process imparts similar properties to various vegetable oils, including olive oil. The researchers determined the minimum inhibitory concentrations (MICs) using agar dilution methods and found that Oleozon exhibited antimicrobial activity against all tested strains, with MICs ranging from 1.18 to 9.5 mg/mL. The study concluded that Oleozon has valuable antimicrobial properties, suggesting its potential as a competitive antimicrobial agent. However, the study did not specifically assess the cytotoxicity of ozonized sunflower oil on human keratinocytes and fibroblasts. Therefore, while the antimicrobial efficacy of ozonated sunflower oil was demonstrated, its safety and biocompatibility concerning human cells were not addressed in this study.

Clinical use of ozonated olive oil has generally been well-tolerated, with few documented adverse events. Notably, no systemic toxicity has been reported from topical/oral use of OOO in dentistry, unlike gaseous ozone therapy, where careful dose control is required. However, some adverse effects have been observed:

- Local irritation and dermatitis: Ozonated oil can cause irritation to the mucosa or skin in susceptible individuals. A recent report highlighted two cases of contact dermatitis (one irritant, one allergic) attributed to topical pharmaceutical ointments containing ozonated olive oil. In one case, OOO applied to the lips caused an inflammatory reaction, likely because the thin mucosa is more sensitive to oxidative irritation. These cases are rare, but they demonstrate that an allergic reaction to OOO is possible. Manufacturers even advise against applying OOO on very thin mucosal areas (like lips) to avoid such irritation [26].
- Transient burning or sensitivity: A mild burning sensation at the application site has occasionally been noted. For instance, in a trial for cutaneous leishmaniasis, ozonated oil caused a transient burning feeling on lesions (resolving quickly) as the only adverse effect observed. In dentistry, Patel et al. (2012) reported a significant increase in dentinal sensitivity in quadrants treated with OOO during periodontal therapy. This suggests OOO's potent oxidizing action might irritate exposed dentin or nerve endings in some cases. Fortunately, such sensitivity is usually temporary [26].

- Unpleasant odor and taste: Ozonated olive oil is described as having a distinctive pungent odor due to oxidative byproducts (ozonides and peroxides). Some patients may find the smell or taste off-putting. This is not a dangerous effect, but a practical consideration for compliance. High-viscosity ozonated oils may also leave a coating sensation. New delivery formulations (e.g., emulsions, encapsulated OOO) are being explored to mitigate these drawbacks (reducing odor, improving texture) [26].

Overall, the literature on the adverse effects of ozonated oils is sparse, and OOO is considered safe for topical use in appropriate concentrations. Unlike ozone gas, which has well-known risks if inhaled or applied in excess (e.g., respiratory irritation, oxidative stress), ozonated oils release ozone gradually and locally, minimizing acute toxicity. Standard precautions include avoiding contact with the eyes and not applying to very sensitive mucosa, as well as monitoring for any allergic reaction on first use [26,27]. Ozonated olive oil exhibits a dual mode of action: potent antimicrobial effects coupled with anti-inflammatory and pro-healing effects. These properties stem from the molecular reactions of ozone with the olive oil matrix and subsequently with biological tissues:

- Sustained release of reactive oxygen species: Ozone (O_3) reacts with unsaturated fatty acids in olive oil to form stable ozonides and peroxides. When OOO is applied to tissues, these ozonides gradually decompose, releasing reactive oxygen species (ROS) and small peroxidic molecules. This creates a localized oxidative environment that is highly bactericidal, virucidal, and fungicidal. Ozone is recognized as one of the most potent broad-spectrum antimicrobials. The ROS attacks microbial cell envelopes, lipoproteins, and DNA. For example, ozone and its byproducts oxidize the phospholipids and proteins in bacterial cell membranes, leading to cell lysis. This mechanism is nonspecific to a particular microbe, so microorganisms (including antibiotic-resistant strains) cannot easily develop resistance to ozone or ozonated oil. Studies show OOO is effective against periodontal pathogens (e.g., *P. gingivalis*, *T. forsythia*), endodontic pathogens like *Enterococcus faecalis*, and *Candida* fungi. Nardi et al.'s trial showed dramatically reduced salivary MMP-8 and bacterial load with OOO, reflecting its antimicrobial/anti-inflammatory impact in vivo [26].
- Anti-inflammatory cytokine modulation: In addition to direct germicidal action, the oxidative burst from OOO triggers biological signaling pathways that modulate the host inflammatory response. The mild ROS stress from ozonides activates the Nrf2 pathway in mammalian cells. Nrf2 is a transcription factor that upregulates antioxidant enzymes (like glutathione peroxidase, superoxide dismutase) and cytoprotective genes. Activation of Nrf2 leads to suppression of NF-κB, a master regulator of inflammation. Consequently, pro-inflammatory cytokines (such as TNF-α, IL-1β, IL-6) and inflammatory mediators like leukotriene B4 are downregulated. Simultaneously, ozone can induce the release of anti-inflammatory cytokines (e.g., IL-10) and growth factors that promote healing. In essence, ozone/OOO causes an initial oxidative stimulus that the body counteracts by generating a robust antioxidant and anti-inflammatory response (hormetic effect). This shift from oxidative stress to an anti-inflammatory state helps reduce tissue redness, swelling, and bleeding. Clinically, this was evidenced by reduced gingival index and bleeding in OOO-treated groups across multiple studies (Choudhary 2024, Nardi 2020) despite high microbial challenge [8, 26–29].
- Enhanced wound healing and blood flow: Ozone has been reported to improve local circulation and oxygen delivery by increasing the flexible deformability of erythrocytes and nitric oxide (NO) production in tissues. Better oxygenation of tissues can aid healing in periodontal and peri-implant lesions. Moreover, OOO's activation of immune cells (such as neutrophils and macrophages) leads to the release of growth factors (TGF-β, PDGF) that stimulate tissue repair and fibroblast

proliferation (although specific studies in a dental context are limited, this mechanism is supported by ozone therapy research in wound healing). Ozone has also been shown to promote a regenerative environment by influencing T-lymphocyte subsets, for instance, by increasing regulatory T cells that help resolve inflammation [27,28].

In combination, these mechanisms mean that ozonated olive oil not only disinfects the area (reducing pathogenic load) but also dampens the inflammatory process and accelerates healing. A practical outcome of this dual action is the significant drop in matrix metalloproteinase-8 (collagenase) levels observed when OOO was used in periodontitis therapy. Lower MMP-8 indicates preservation of connective tissue, likely due to reduced neutrophil hyperactivity in an environment of diminished inflammation. Patients treated with OOO have shown improvements in clinical attachment and reduced bleeding on probing, consistent with an anti-inflammatory benefit. It should be noted that OOO's effects are local; the systemic absorption of ozone byproducts is minimal when used topically, so its systemic anti-inflammatory effects are limited. However, locally in the gingival or pulpal tissues, OOO provides a potent combination of disinfection and inflammation control without relying on antibiotics or steroids. This makes it particularly appealing in periodontal therapy and healing of oral wounds, where managing bacterial burden and inflammation simultaneously is crucial [27–29].

Thus, the literature supports the potential of OOO as an adjunctive treatment in various dental applications, including antimicrobial therapy, periodontal therapy, management of dentin hypersensitivity, and endodontic applications. Its antimicrobial, anti-inflammatory, and healing properties, and its safety and biocompatibility make it a promising agent in dental therapy. In managing peri-implant mucositis, the application of OOO gel has led to significant reductions in clinical inflammation parameters, such as bleeding on probing and probing depth, thereby contributing to the long-term stability of implants. Combining OOO with root canal filling materials has shown promising results in improving radiopacity and reducing periapical inflammation, highlighting OOO's potential as a viable alternative in pediatric dentistry. In periodontal therapy, OOO-based mouth rinses have demonstrated superior clinical and biochemical improvements compared to mechanical therapy alone, suggesting a significant role in managing periodontal inflammation. Regarding dentin hypersensitivity, OOO, when combined with sodium calcium phosphosilicate, has shown greater effectiveness in reducing post-operative discomfort. However, further research, including large-scale randomized controlled trials and long-term studies, is warranted to establish standardized protocols and confirm its efficacy across diverse patient populations.

5. Conclusions

In conclusion, the findings of this study indicate that OOO presents as a promising therapeutic option in modern dentistry, with the potential to enhance clinical outcomes in various contexts. Demonstrating effectiveness in different clinical applications, OOO stands out as an innovative and versatile therapeutic agent in dentistry. Evidence gathered from multiple clinical studies suggests that OOO possesses potent antimicrobial properties and offers significant benefits in reducing inflammation and promoting tissue healing. As research supports its efficacy, ozonated olive oil will likely play an increasingly prominent role in dental practice, supporting safer, more effective, and minimally invasive treatment protocols for a wide range of oral health conditions.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Authors' contributions

C.D.A., F.Ga. conceptualized the study; V.R. and C.D.A. analyzed and interpreted the data; V.R., F.A., F.Go., G.C. wrote and reviewed the manuscript; T.N., G.C. supervised the project and contributed to the manuscript preparation. All authors agreed on the final version of the manuscript.

Conflict of interest

Cesare D'Amico and Francesca Gorassini are editorial board members for *Journal of Dentistry and Multidisciplinary Sciences*, and they were not involved in the editorial review or the decision to publish this article. The authors declare no conflict of interest.

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